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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,498	01/30/2002	Jong-Gu Park	57354-00002	5213

7590 07/28/2004

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,498	PARK ET AL.	
	Examiner	Art Unit	
	J. D. Schultz, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,23,30-39,41,42 and 46-61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,23,30-39,41,42 and 46-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 3, 2004 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed May 3, 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed December 5, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments, Claim rejection, 35 U.S.C. § 102

The rejection of claims 30, 31, 33-37, and 39 under 35 U.S.C. 102(b) as being anticipated by Hellmannn et al. (Virology. 1985 143:23-34), is withdrawn in view of applicants' amendment reciting a limitation not found in Hellmann, namely that the instantly claimed antisense constructs are in composition with a lipid carrier.

The rejection of claims 23 and 42 under 35 U.S.C. 102(b) as being anticipated by Moon et al. has been withdrawn. The withdrawal is based on the length limitation of the present claims, whereby the antisense nucleic acid constructs must be "at least about 3000 nucleotides". The constructs of Moon *et al.* are much shorter, approximately 150 nucleotides, which is not reasonably considered to be at least about 3000.

The rejection of claims 23, 30-32, and 42 under 35 U.S.C. 102(b) as being anticipated by LaPlante et al. (Biochem J. 2000. 348:189-199) is withdrawn in view of applicant's arguments. The claims recite "a composition comprising a chimeric large circular single stranded nucleic acid molecule", which had been interpreted as reading on a double stranded nucleic acid molecule, given the use of the open, "comprising" language. However, because the specification contemplates the use of only single stranded nucleic acids, and further, since the strands of a double stranded nucleic acid are bonded, albeit through weak, hydrogen bonds, the double stranded molecules are interpreted herein as constituting a separate molecule than the single stranded molecules as instantly claimed.

Response to Arguments, Claim Rejections - 35 USC § 103

The rejection of claims 22, 23, 46 and 47 under 35 U.S.C. 103(a) as being unpatentable over Hellmann et al., in view of Hu et al. (U.S. Patent Number 6,107,062) is withdrawn in view of the amendment to the claims reciting the limitations that the constructs of claims 22, 23, 46 and 47 must be in compositions comprising liposomes and pharmaceutically acceptable carriers thereof, which is not taught or suggested by this particular combination of references.

The rejection of claims 38, 46, and 47 under 35 U.S.C. 103(a) as being unpatentable over Hellmann et al., in view of Moon et al., and LaPlante et al. is maintained for the same reasons of record as cited in the Official action dated December 5, 2003. However, applicants have amended the remaining claims such that the art cited instantly becomes applicable against the broader set of claims. Therefore, while this rejection is maintained and argued below, a new rejection under 35 U.S.C. § 103(a) is set forth that is based on art cited in the instant rejection, and moreover encompasses both the instant claims and other claims as discussed in the new rejection under 35 U.S.C. § 103(a).

Applicants argue that the rejection of claims 38, 46, and 47 under 35 U.S.C. 103(a) as being unpatentable over Hellmann et al., in view of Moon et al., and LaPlante et al. is untenable because a *prima facie* case of obviousness has not been established. Applicants indicate that while Hellmann *et al.* discloses a single stranded M13 vector that comprises an antisense region, Hellmann *et al.* does not disclose the antisense region comprising a full-length gene and a liposome transfection system. According to applicants, LaPlante fails to motivate one of ordinary skill to use the M13 construct comprising a partial antisense region of Hellmann *et al.* with the full length antisense region of LaPlante.

This is not considered convincing, because Moon *et al.* teaches that circular antisense molecules such as that taught by both Moon and Hellmann are nuclease resistant and are effective as inhibitors of protein expression, and because LaPlante *et al.* teach that full length antisense transcripts are known to those of ordinary skill in the art to be used in determining the effects of protein knockout on the function of that protein. Because one of ordinary skill in the art would be motivated to make antisense constructs that help determine the function of a protein as evidenced by all of Moon, Hellmann and LaPlante, and because both long and short antisense transcripts are commonly used as evidenced by the above combination of references, the length of the antisense transcript is considered to be merely a design choice. Since LaPlante teaches using long, antisense transcripts to inhibit protein expression in order to study cell proliferation and DNA synthesis, and because one would be further motivated to modify such antisense molecules to increase their bioactivity such as those taught by Moon and Hellmann that are nuclease resistant, one of skill would be motivated to modify the M13 construct comprising a partial antisense region of Hellmann *et al.* by inserting the full length antisense region of LaPlante.

Applicants further argue that although the circular antisense constructs of Moon *et al.* are taught in liposomes, one of skill would not be motivated to place the circular antisense constructs of Hellmann into a liposome. Applicants assert that this is true because "there is no disclosure or suggestion present in Hellmannn for a need for a liposome in its assay system because Hellmannn is satisfied with its system and Hellmannn has no purpose or reason for transfecting any cell with its single-stranded M13." Applicants also assert that Moon fails to disclose or

suggest that the liposome transfection system will be functional with a single- stranded nucleic acid which is at least about 3,000 bases long or a phage genome.

Taking the last point first, Moon et al. indeed suggest that a liposome transfection system will be functional with a single- stranded nucleic acid which is at least about 3,000 bases long or a phage genome. Moon *et al.* teach at the 2nd to last paragraph on page 4652 that a meaningful level of oligo uptake should be consistently obtainable when carried into cells by liposomes, regardless of the size of the oligo. Regarding whether one would be motivated to combine the large nucleic acid of Hellmannn with liposomes as taught by Moon, it is reiterated that both Moon *et al.* and Hellmann *et al.* teach antisense inhibition of protein expression using large circular nucleic acids. Since Moon clearly states that "the relatively large size of RiAS oligos should not pose a problem for efficient cellular uptake", and since the nucleic acids of both Moon *et al.* and Hellman *et al.* are shown to be efficient at inhibiting protein expression, and because Moon *et al.* show that one of ordinary skill prefers to use large circular antisense nucleic acids in liposomes to increase cellular transfection, it would have been obvious to one of ordinary skill in the art to use liposomes to assist in transfecting cells with such nucleic acids.

Claim Rejections - 35 USC § 112

Claims 41 and 42 (by dependency) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 41 recites the limitation "said genes" when there is no previous reference in the claim to said genes. Thus, there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

Claims 22, 23, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellmann et al., in view of Moon et al., LaPlante et al., Hu et al. (all of record), and Gewirtz *et al.* (Proc. Natl. Acad. Sci. 1996. v 93, pp.3161-3163).

The invention of the above claims is drawn to a composition comprising a large circular nucleic acid comprising a target specific antisense region or a plurality of such regions wherein said antisense molecule is effective for reducing the expression of said gene and a transfection effective carrier comprising a lipid carrier which may optionally be a liposome, wherein said large nucleic acid is about at least about 3000 nucleotides long, or wherein said antisense region is at least about 50 nucleotides long, or wherein said antisense region is substantially complementary to an entire gene sequence, or is a single stranded form of a recombinant bacteriophage or phagemid genome, or is derived from a filamentous phage, which may be M13, or a vector or host cell comprising said large circular nucleic acid.

Hellmann et al. teach a large circular nucleic acid comprising a target specific antisense region that specifically binds to a portion of RNA expressed from a gene, wherein said antisense molecule is effective for reducing the expression of said gene, wherein said large nucleic acid is about at least about 3000 nucleotides long, wherein said antisense region is at least about 50 nucleotides long, and is a single stranded recombinant bacteriophage or phagemid genome that may optionally be M13, a cell and a vector comprising said large circular nucleic acid, and wherein said large nucleic acid comprises a pharmaceutical carrier. Hellmann *et al.* does not teach a large circular nucleic acid in combination with a transfection effective carrier comprising

a lipid (i.e. a liposome), or such nucleic acids containing more than one antisense region, or a full length antisense construct.

Moon et al. teach a large circular nucleic acid comprising more than one antisense region wherein the large circular antisense molecule is effective for reducing the expression of said gene, wherein said antisense region is at least about 50 nucleotides long, and is in combination with a eukaryotic cell transfection effective carrier comprising a lipid, further comprising a pharmaceutical carrier, and such compositions comprising a host cell.

LaPlante et al. teaches a large circular nucleic acid molecule comprising a target specific antisense region that is fully complementary to an entire gene sequence.

Hu et al. discloses targeting multiple genes within the HIV-1 genome (col. 4, lines 5-15) using plasmids containing multiple antisense sequences targeted to distinct regions of said genome.

Gewirtz *et al.* teach that methods of delivering nucleic acids to cells, including the use of liposomes and polycationic lipids to promote such delivery, are well known to those of ordinary skill in the art.

It would have been obvious to one of ordinary skill in the art to make compositions comprising the large circular nucleic acid constructs of Hellmann *et al.* with a liposome as taught by either of Moon, and Gewirtz, because Hellmann teaches that large circular nucleic acid constructs efficiently block protein expression, and because both of Moon and Gewirtz teach that liposomes are commonly used in the art to increase the ability of nucleic acids to penetrate the cell membrane and thus achieve higher intracellular concentrations, and achieve better inhibition of protein expression. One of skill would have had a reasonable expectation of success in making

such constructs because both Moon and Gewirtz teach the methods of doing so, which are routine to one of ordinary skill in the art.

Furthermore, It would have been obvious to one of ordinary skill in the art to modify the construct of Hellmann containing one antisense nucleic acid region to contain multiple antisense regions as taught by both Moon *et al.* and Hu *et al.*, because both teach large nucleic acid constructs comprising multiple antisense regions and that making such inhibitory nucleic acids with multiple antisense regions are preferred because they possess an increased number of binding sites for greater inhibition of protein expression. One would have had a reasonable expectation of success in making and using such nucleic acids, because the methods of both Moon and Hu would suffice in making them, and because Moon teaches how to use them, and because all such steps are routine the person of ordinary skill. Thus, in the absence of evidence to the contrary, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the absence of evidence to the contrary.

Double Patenting

Applicant is advised that should claims 33 and 39 be found allowable, claim 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz, Ph.D. whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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